REMARKS

Claims 1-14 are in the present application. The claims are provided in an attached appendix for the Examiner's convenience.

REJECTIONS UNDER 35 U.S.C. § 102

Claims 1-2, 10-13 and 14 "stand rejected under 35 U.S.C. 102(b) as being anticipated by Claffey et al. (Biochim. Biophys. Acta. 1246(1): 1-9, 1995) for the reasons of record in paper #5". Of note, Paper No. 5 is an Amendment mailed by Applicants January 2, 1998. According to Paper No. 2, Claffey et al. teach the mutation of cysteine residues in murine vascular endothelial growth factor (VEGF) to serine residues at various locations in the VEGF molecule and that although no binding activity is shown, since some stimulation is shown, one would expect binding activity. Applicants respectfully traverse.

Claffey et al. teach cysteine to serine mutations in murine VEGF. Although it was shown that these mutants were less active than wild-type VEGF, no experiments were performed which measured the antagonistic effect of these mutations. The Examiner argues that since some of these mutants "appear to have some stimulatory activity, the skilled artisan would reasonably expect these mutants to also bind the VEGF receptor, making the VEGF mutants of Claffey antagonists, absent clear and convincing evidence to the contrary." The clear and convincing evidence to the contrary is provided by Potgens et al.

The VEGF mutants made by Potgens and Claffey are similar in that the corresponding cysteines, in human VEGF and murine VEGF, respectively, are converted to serines. On page 32883, describing the only assays directly measuring an antagonistic effect, Potgens shows in both a mitotic assay and a vascular

permeability assay that the mutants did not inhibit the activity of the wild type protein, and thus had no antagonistic activity. In Fig. 8 of the specification, the present invention shows a direct antagonistic effect on wild type VEGF activity. Thus, the activity of these mutants are clearly different. Moreover, the claimed invention recites that the "antagonistic molecule is capable of inhibiting a biological activity of a native VEGF protein, wherein said biological activity is induction of a VEGF response." The mutants of Claffey do not have this effect. Anticipation requires each and every element be disclosed in a single cited reference. Since this is not the case, Claffey does not anticipate the present invention.

Claims 1-3, 10-12, and 14 "stand rejected under 35 U.S.C. 102(b) as being anticipated by Potgens et al. (J. Biol. Chem. 269(52): 32879-32885, 1994) for the reasons of record in paper #5." Applicants respectfully traverse.

The Office Action states that the VEGF mutants of Potgens demonstrate an ability to bind the VEGF receptor and demonstrate decreased activity. This is not the same as having an antagonistic effect. As discussed above, the mutants of Potgens do not have such an effect. As the claims are directed to a VEGF mutant that inhibits induction of a VEGF response, and anticipation requires that each and every element be disclosed by a cited reference to anticipate, Potgens does not anticipate the present invention.

In Paper No. 23, the Office Action further states that the C2S and C4S mutants of Potgens are structurally the same proteins as what is being claimed and therefore must have the same functional activity. Applicants submit that this is not the case.

Applicants have provided examples of amino acid changes such as those, for example, indicated in Claims 4-6 wherein a cysteine is substituted with an aspartic

acid. Potgens (and Claffey) describe VEGF mutants involving cysteine to serine changes. Furthermore, the variants which are claimed are those which possess different biological activities than those of Potgens and Claffey. The mutants of Potgens do not inherently have antagonistic activity, because Potgens shows that they do not. Thus, the present invention is distinct from the prior art. Applicants therefore respectfully request withdrawal of the rejection.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 4-6 and 9 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Potgens et al. as applied to claims 1-3, 10-12, and 14 for the reasons of record in paper #5.

Claims 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Potgens et al. as applied to claims 1-3, 10-12, and 14 in view of Pang (U.S. Pat. No. 5,418,135) for the reasons of record in paper #5.

Claim 13 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Potgens et al. as applied to claims 1-3, 10-12, and 14 for the reasons of record in paper #5.

To find obviousness, (1) the prior art must teach or suggest all of the claim limitations, (2) there must be a suggestion in the references to combine the cited references, and (3) there must be a reasonable expectation of arriving at the claimed invention by combining the references. (*see generally*, MPEP §2143)

As discussed above, the prior art does not teach or suggest all the claim limitations. In particular, the prior art does not teach VEGF mutants which act as VEGF antagonists by inhibiting induction of a VEGF response. In fact, the prior art

teaches away from the invention, by showing that VEGF mutants which contain cysteine to serine substitutions do not act as VEGF antagonists.

Nor does the combination with Pang overcome this failing. Pang merely teaches chemical modifications of cysteine residues. Pang does not suggest that VEGF mutants, particularly cysteine to serine mutants, can act as VEGF antagonists. Applicants therefore respectfully request withdrawal of the rejection.

On the basis of the amendment and remarks presented herein, we believe that this application is now in condition for immediate allowance and respectfully request the Examiner to make such a finding and pass this application to issue.

Respectfully submitted,

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APPENDIX

1. (Thrice Amended) A vascular endothelial cell growth factor (VEGF) antagonist molecule comprising a variant VEGF polypeptide, said variant polypeptide comprising an amino acid modification of at least one cysteine residue, wherein said amino acid modification inhibits the ability of said variant polypeptide to properly dimerize with another VEGF polypeptide monomer, wherein said antagonist molecule is capable of binding to VEGF receptors without significantly inducing a VEGF response, wherein said antagonist molecule is capable of inhibiting a biological activity of a native VEGF protein, wherein said biological activity is induction of a VEGF response.

2. The antagonist molecule according to Claim 1 wherein said amino acid modification is a substitution of said at least one cysteine residue with a different amino acid which is incapable of participating in a disulfide bond.

3. The antagonist molecule according to Claim 2 wherein said substitution is of the cysteine residue at amino acid position 51 and/or 60 of the native VEGF amino acid sequence.

4. The antagonist molecule according to Claim 3 wherein aspartic acid is substituted for cysteine.

5. The antagonist molecule according to Claim 4 comprising the substitution C51D.

6. The antagonist molecule according to Claim 4 comprising the substitution C60D.

7. The antagonist molecule according to Claim 1 wherein said amino acid modification is a chemical modification of said at least one cysteine residue which renders said cysteine residue incapable of participating in a disulfide bond.

8. The antagonist molecule according to Claim 7 wherein said chemical modification is of the cysteine residue at amino acid position 51 and/or 60 of the native VEGF amino acid sequence.

9. The antagonist molecule according to Claim 1 containing further amino acid modifications that do not otherwise affect the essential biological characteristics.

10. An isolated nucleic acid sequence comprising a sequence that encodes the VEGF antagonist molecule of Claim 1.

11. A replicable expression vector capable in a transformant host cell of expressing the nucleic acid of Claim 10.

12. Host cells transformed with the vector according to Claim 11.

13. Host cells according to Claim 12 which are Chinese hamster ovary cells.

14. A composition of matter comprising the VEGF antagonist molecule according to Claim 1 compounded with a pharmaceutically acceptable carrier.